PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1332 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/033268	International filing date *(day/month/year)* 07.10.2004	Priority date *(day/month/year)* 08.10.2003
International Patent Classification (IPC) or national classification and IPC A61K47/12, A61K9/08, A61K31/4458		
Applicant MALLINCKRODT INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.08.2005	02.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hedegaard, A Telephone No. +49 89 2399-8644

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033268

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-8	as originally filed

Claims, Numbers

8-18, 19(part), 27-31, 33-44, 45(part)	as originally filed
1-5, 7, 19(part), 20-24, 26, 45(part), 46-50	received on 01.08.2005 with letter of 01.08.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033268

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24, 26-31, 33-34,50

because:

☒ the said international application, or the said claims Nos. 24, 26-31, 33-34,50 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. -

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033268

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5, 7-24, 26-31, 33-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	9-23, 35-49
	No:	Claims	1-5,7-8, 24, 26-31, 33-34,50
Industrial applicability (IA)	Yes:	Claims	1-5, 7-23, 35-49
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 24, 26-31, 33-34 and 50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D1 (see paragraph [0024]) discloses nasal solutions comprising methylphenidate, ascorbic acid and non-aqueous solvent such as propylene glycol.

2. The subject-matter of independent claims 1 and 24 is novel (Art. 33(2) PCT) since there is no disclosure in any of the available prior art documents of methylphenidate solutions comprising an organic acid selected from the group of acetic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and mixtures thereof.

3. The subject-matter of independent claims 9, 14, 19, 35, 40 and 45 is novel (Art. 33(2) PCT) since there is no disclosure in any of the available prior art documents of methylphenidate solutions comprising at least one organic acid and a solvent system comprising water, polyol and glycol in the amounts as defined in said claims.

4. The subject-matter of independent claim 50 is novel (Art. 33(2) PCT) since there is no disclosure in any of the available prior art documents of the use of methylphenidate solutions comprising an organic acid for oral or intravenous administration.

5. The subject-matter of independent claims 9, 14, 19, 35, 40 and 45 differs from D1 (closest prior art) in specifying a certain amount of organic acid and in defining a solvent system comprising water, polyol and glycol in certain amounts.

   The problem of the present applications was to provide methylphenidate solutions that are chemically stable, pharmaceutically acceptable and palatable. There is no hint in any of the available prior art documents that this problem is solved by the compositions as defined in said independent claims.

   Therefore, the subject-matter of claims 9-23 and 35-49 is considered to involve an inventive step (Art. 33(3) PCT).

6. The subject-matter of independent claims 1, 24 and 50 differs from D1 (closest prior art) in specifying certain organic acids or in the way of administration. However, these features do not appear to be accompanied by any non-obvious effects and can be carried out by the skilled person without having to resort to inventive skill (Art. 33(3) PCT).

   Additionally, claims 1, 24 and 50 do not share a single general inventive concept with the group of independent claims 9, 14, 19, 35, 40 and 45. Hence, the requirements of Rule 13.1 PCT are not met.

7. A positive international preliminary report for the subject-matter of the dependent claims 2-5, 7-8 and 26-34 can only be established when they refer to independent claims which meet the requirements of the PCT.

8. For the assessment of the present claims 24, 26-31, 33-34 and 50 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Section VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Re Section VIII

Certain observations on the international application

1. The word "about", particularly when applied to a range, detracts from the general clarity and should be deleted throughout the description and claims (Art. 6 PCT).

2. The last paragraph p. 8 is a general expression which implies that the extent of protection may be expanded in some vague and not precisely defined way and should be deleted (Art. 6 PCT).

CLAIMS

1. A methylphenidate solution comprising:

methylphenidate; and

at least one pharmaceutically acceptable organic acid selected from the group consisting of acetic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and mixtures thereof,

wherein the methylphenidate and the at least one organic acid are dissolved in a solvent system and the solvent system comprises at least one non-aqueous solvent.

2. The methylphenidate solution according to claim 1, wherein the at least one organic acid is present in the methylphenidate solution from about 0.5 mg/ml to about 5.0 mg/ml.

3. The methylphenidate solution according to claim 1, wherein the solvent system further comprises water.

4. The methylphenidate solution according to claim 3, wherein the water is up to 50% of the solvent system.

5. The methylphenidate solution according to claim 1, wherein the at least one non-aqueous solvent is from about 50% to about 100% of the solvent system.

7. The methylphenidate solution according to claim 1, wherein the at least one non-aqueous solvent is selected from the group consisting of polyols, glycols and mixtures thereof.

about 45% to about 55% of at least one polyol solvent; and
about 10% to about 20% of at least one glycol solvent.

20. The methylphenidate HCl solution according to claim 19, wherein the at least one organic acid includes citric acid.

21. The methylphenidate HCl solution according to claim 19, wherein the at least one polyol solvent includes glycerin.

22. The methylphenidate HCl solution according to claim 19, wherein the at least one glycol solvent includes polyethylene glycol.

23. The methylphenidate HCl solution according to claim 19, further including at least one pharmaceutical additive selected from the group consisting of flavorings, colorants, buffer, preservatives and mixtures thereof.

24. A method of treating a patient for a disorder treatable by methylphenidate which comprises administering a therapeutically effective amount of methylphenidate in a liquid solution, wherein the liquid solution comprises:

methylphenidate and at least one pharmaceutically acceptable organic acid selected from the group consisting of acetic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and mixtures thereof,

wherein the methylphenidate and the at least one organic acid are dissolved in a solvent system and the solvent system comprises at least one non-aqueous solvent.

26. The method of treating a patient for a disorder treatable by methylphenidate according to claim 24, wherein the administering of the methylphenidate in a liquid solution is selected from the group consisting of oral administration, intravenous administration and inhalation administration.

dissolving the of methylphenidate HCL and about 0.5mg/ml to about 1.5 mg/ml of at least one organic acid in a solvent system, the solvent system comprising:

about 30% to about 40% water;

about 45% to about 55% of at least one polyol solvent; and

about 10% to about 20% of at least one glycol solvent.

46. The method for producing a methylphenidate HCl solution according to claim 45, wherein the at least one organic acid is selected from the group consisting of acetic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and mixtures thereof.

47. The method for producing a methylphenidate HCl solution according to claim 45, wherein the at least one polyol solvent is selected from the group consisting of glycerin, sorbitol, sucrose, fructose and mixtures thereof.

48. The method for producing a methylphenidate HCl solution according to claim 45, wherein the wherein the at least one glycol solvent is selected from the group consisting of propylene glycol, polyalkylene glycol products and mixtures thereof.

49. The method for producing a methylphenidate HCl solution according to claim 45, further including dissolving at least one pharmaceutical additive selected from the group consisting of flavorings, colorants, buffers, preservatives and mixtures thereof into the methylphenidate solution.

50. A method of treating a patient for a disorder treatable by methylphenidate which comprises administering a therapeutically effective amount of methylphenidate in a liquid solution wherein the liquid solution comprises:

methylphenidate and at least one organic acid in a solvent system, wherein the solvent system includes at least one non-aqueous solvent.

wherein the administering of the liquid solution is selected from the group consisting of oral administration and intravenous administration.